REPLENISH Trial: Endometrial Safety with a 17β-Estradiol and Progesterone Combination (TX-001HR) in Postmenopausal Women with Vasonotor Symptoms

David F Archer, MD; Rogerio Lobo, MD; Risa Kagan, MD; Ginger Constantine, MD; James H Pickar, MD; Gina Gasper, BA; Sheilli Graham, PhD; Brian Bernick, MD; Sebastian Mirkin, MD

Clinical Research Center, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA; Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY; University of California, San Francisco and Salient East Bay Medical Foundation, Berkeley, CA; Endomirin Consultancies, LLC, Malvern, PA; TherapeuticsMD, Boca Raton, FL

Introduction
- Hormone therapy for postmenopausal women with an intact uterus requires the addition of a progestogen to prevent endometrial hyperplasia and reduce the incidence of endometrial cancer
- Use of compounded bio-identical hormone therapy (CBHT) has become highly prevalent in the US since the 2002 published report of the Women's Health Initiative
- An estimated 1 to 2.5 million US women use unapproved CBHT products

Objectives
- All women completed daily diaries
- An estimated 1 to 2.5 million US women use unapproved CBHT products

Methods
- Study Design and Population
  - REPLENISH (NCT01940268) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that evaluated various daily, oral doses of TX-001HR in postmenopausal women with an intact uterus (Tables 1 and 2)

Results
- Table 1. Key inclusion and exclusion criteria

Endometrial Safety Endpoints
- The primary safety endpoint was the incidence of endometrial hyperplasia at month 12
- The incidence of endometrial hyperplasia, per FDA guidance, was planned to be ≤ 1% with an upper bound of one-sided 95% CI ≤ 6%
- Biscopae were centrally and serially read by 3 independent pathologists
- Endometrial hyperplasia was diagnosed with a consensus of 2 of 3 pathologists

Endometrial hyperplasia incidence at all treatments was 0% (Table 4)
- No endometrial cancer was found
- Active and disordered proliferation at 12 months ranged from 0.3% to 2.9% with TX-001HR (Figure 2A)
- Endometrial polyp incidence at 12 months ranged from 1.4% to 3.3% with TX-001HR (Table 4)

Conclusions
- This TX-001HR clinical trial provided evidence of endometrial safety
  - AITX-001HR doses had 0% incidence of endometrial hyperplasia, achieving the ≥1% incidence (1-sided, upper 95% CI <1%) as per FDA guidance
  - No endometrial malignancies were found
- The absence of endometrial hyperplasia and endometrial cancer in this study should be considered in light of case reports of endometrial hyperplasia and endometrial cancer observed with CBHT
- Endometrial safety was also confirmed with TX-001HR underscoring the need for CBHT safety studies given their potential risks
  - If approved, TX-001HR may be an appropriate alternative combination HT with E2/P4 for treating VMS, especially in the estimated millions of postmenopausal women currently using less regulated and unapproved CBHT

References